

EVALUATION OF ANTINOCICEPTIVE ACTION OF PENTAZOCINE IN COMPARISON WITH MORPHINE IN ALBINO RATS

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ABSTRACT: OBJECTIVES: To evaluate the antinociceptive effect of pentazocine in three graded doses (3, 6 and 12 mg/kg) and its combination with morphine at sub-analgesic doses, and comparing their effect with analgesic dose of morphine (1mg/kg) by tail flick method in albino rats. **MATERIALS & METHODS:** Tail flick method using analgesiometer and tail immersion test by hot water bath was selected for evaluating antinociceptive action of pentazocine and standard drug morphine. **RESULTS:** Pentazocine in the doses of 6mg/kg, 12 mg/kg intra peritoneal (i.p) and morphine 1mg/kg i.p, produced significant antinociceptive effect in comparison to control by tail flick test and tail immersion test. Pentazocine 3 mg/kg, i.p and morphine 0.1 mg/kg, i.p had not produced significant antinociceptive action when given alone, but combination (pentazocine 3 mg/kg + morphine 0.1 mg/kg) treatment produced significant antinociceptive effect in comparison to control. **CONCLUSION:** Pentazocine in the doses of 6 mg/kg, 12 mg/kg and their combination in low doses (pentazocine 3 mg/kg + morphine 0.1 mg/kg) demonstrated significant antinociceptive activity in albino rats. Combination in low doses (pentazocine 3 mg/kg + morphine 0.1 mg/kg) showed comparable antinociceptive activity with pentazocine 6 mg/kg in albino rats. **STATISTICAL ANALYSIS:** One way ANOVA and multiple comparison test (LSD) was applied only to MPE% at 60 min.

KEYWORDS: Antinociception, Pentazocine, Morphine, Tail flick test, Tail immersion test, Albino rats.

INTRODUCTION: The taxonomy committee of International Association for the study of pain defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."⁽¹⁾ Pentazocine, an opioid analgesic, is widely used for the management of pain in humans^(2,3,4) and it acts as an agonist to μ and κ receptors and as a weak antagonist to μ opioid receptor.^(5,6) It has been reported that pentazocine dose-dependently potentiated morphine induced analgesia in non-opioid-tolerant patients with chronic pain⁽⁷⁾ and that the combination of pentazocine with morphine produced a significantly greater level of analgesia than each opioid analgesic alone in patients undergoing surgery for the removal of impacted wisdom teeth.⁽⁸⁾ On the other hand, Houde RW et al in 1970 reported that pentazocine antagonized morphine induced analgesia in opioid-tolerant patients with chronic pain.

It has also been reported that pentazocine did not influence the analgesic effect of morphine on abdominal operative pain⁽⁹⁾ and that of Pethidine, an opioid analgesic, on pressure-induced somatic pain.⁽¹⁰⁾ In experimental animal studies, Harrs LS, Pierson AK 1964 & Pearl J, Pierson 1966 were reported that pretreatment with pentazocine antagonized morphine or Pethidine-induced antinociception in the rat tail-flick test,⁽¹¹⁾ on the other hand Shimada A et al in 1984 reported, simultaneous treatment with pentazocine had a synergistic effect in the mouse tail pressure and

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acetic acid writhing, and an antagonistic effect in the mouse tail pinch test, depending upon the dose of each drug.⁽¹²⁾ Further Hiroki Hamura et.al 2000 also reported synergistic effect between pentazocine and morphine in rat tail immersion test.⁽¹³⁾ Hence the present study is undertaken in the experimental rat model for evaluating antinociceptive potential of pentazocine and its combination with morphine at their sub analgesic doses.

MATERIALS& METHODS:

ANIMALS: Wistar Albino Rats (150-200grms), housed under standard laboratory conditions, maintained on 12:12 light dark cycle and had free access to food and water.

DRUGS AND CHEMICALS: 1. Pentazocine lactate (Fortwin) – Ranbaxy laboratories Ltd. Ahmadabad, India. 2. Morphine sulphate (Rumorf) – Rusan pharma Ltd. India.

MODELS FOR PAIN:

1. Pain induced by generating Radiant type of heat by using Analgesiometer in Albino Rats.
2. Pain induced by direct type of heat of Thermal type by Hot Water Bath method in Albino Rats.

TAIL FLICK TEST BY ANALGESIOMETER⁽¹⁴⁾: Wistar albino rats of either sex were selected by process of randomization and which shows reaction time of less than 6 sec are used for experimental purpose. They are weighed and divided in to 7 groups containing 6 animals in each group. The tail flick latency was measured at 0 minute, i.e. immediately after giving the drug, and then successively at 15, 30, and 60 min of duration after drug administration. Normal saline (NS) used as control. The antinociceptive activity was considered as positive when reaction time is more than 6 sec and within 10 sec. Cut-off time is 10 sec in order to prevent the damage to the rat tail.

TAIL IMMERSION TEST BY HOT WATER-BATH⁽¹⁵⁾: Wistar albino rats of either sex had been selected by the process of randomization and which showed reaction time of less than 6 sec was used for experimental purpose. Rats were weighed and divided into 7 groups containing 6 animals in each group. The tail withdrawal latency was measured i.e. at 0 minute, i.e. immediately after giving the drug, and then successively at 15 min, 30 min, 60 min of duration after drug administration. Tail withdrawal latency is the time duration from immersing the tail in hot water bath, which is maintained at 55±0.5°C temperature by using thermostat control, till the withdrawal of the tail from hot water bath. Normal saline treatment used as control. The antinociceptive activity was considered as positive when reaction time is more than 6 sec and within 15 sec. Cut-off time was 15 sec to prevent the damage to the rat tail.

OBSERVATION & RESULTS:

Maximum Possible Effect (MPE) in percentage = $(\text{post drug latency} - \text{pre drug latency} / \text{cut-off time} - \text{pre drug latency}) \times 100$.

Tail flick Method: Tail flick latency (sec) was recorded at 0, 15, 30 and 60 min after drug administration. From the observed data the maximum possible effect in percentage of increased tail flick latency at 60 min is calculated for each group.

Maximal possible effect (MPE) of tail flick latency in percentage (%) at 60 min was calculated in Pentazocine 6, 12 mg/kg, Morphine 1 mg/kg and combination group (Pentazocine 3 mg/kg + Morphine 0.1 mg/kg) (55.72±4.76, 75.85±3.18, 95.24±2.38, 55.08±3.96 respectively) which is more

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and statistically significant in comparison to control group (6.14 ± 2.98) (Table no.1). These results suggest that Pentazocine 6, 12 mg/kg, Morphine 1 mg/kg and combination treatment can produce significant antinociceptive effect. Comparison of MPE (%) of Pentazocine 12 mg/kg (75.85 ± 3.18) with Morphine 1 mg/kg (95.24 ± 2.38) (Table no.1), indicating that Morphine is more potent than Pentazocine. MPE (%) in combination group (55.08 ± 3.96) is significantly more than Pentazocine 3 mg/kg (14.79 ± 4.89) alone or Morphine 0.1 mg/kg (4.52 ± 2.24) alone indicating Pentazocine can potentiate antinociceptive effect of Morphine (Table no.1 and 2). Table no:1 MPE in % of increased tail flick latency.

SL. NO	NS	MOR 0.1	MOR 1	PTZC 3	PTZC 6	PTZC 12	PTZC 3+ MOR 0.1
1	0	13.33	100	33.33	53.84	76.92	53.84
2	0	6.66	92.85	20	73.33	66.66	50
3	0	0	100	7.69	38.46	84.61	57.14
4	14.29	7.14	92.85	0	50	83.33	46.15
5	7.14	0	100	7.69	61.53	66.66	73.33
6	15.38	0	85.71	20	57.14	76.92	50
Total	36.81	27.13	571.41	88.71	334.3	455.1	330.46
Mean	6.14	4.52	95.24	14.79	55.72	75.85	55.08
SD	7.29	5.48	5.83	11.98	11.66	7.80	9.70
SE	2.98	2.24	2.38	4.89	4.76	3.18	3.96
NS - Normal Saline, MOR- Morphine, PTZC - Pentazocine							
Table 1							

Figure 1: Graph showing MPE of increased tail flick latency in % of normal saline, Morphine, Pentazocine and combination groups.

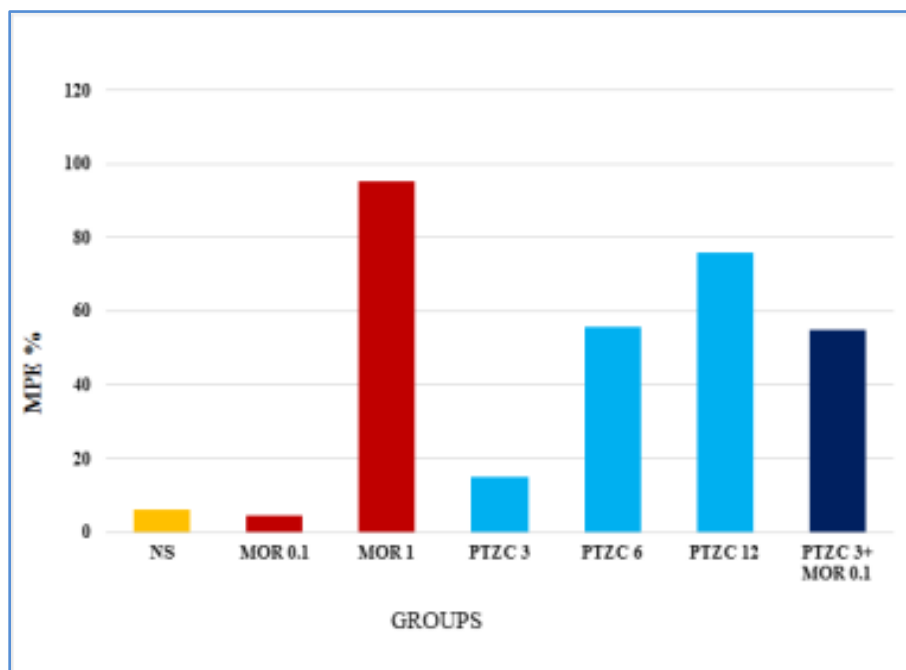


Figure 1

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Comparison between different groups	Mean Difference	p Value
NS vs MOR 0.1	1.61	.755 ns
NS vs MOR 1	-89.10	<.0001***
NS vs PTZC 3	-8.65	.100 ns
NS vs PTZC 6	-49.58	<.0001***
NS vs PTZC 12	-69.71	<.0001***
NS vs PTZC 3 + MOR 0.1	-48.94	<.0001***
NS-Normal Saline, MOR-Morphine, PTZC- Pentazocine ns-not significant, **** Highly Significant		
Table 2: Intergroup comparison of MPE in % of Pentazocine Tail Flick latency by multiple comparison (LSD) test.		

TAIL IMMERSION METHOD: Tail withdrawal latency (sec) after immersing tail in hot water ($55\pm 0.5^{\circ}\text{C}$) was recorded at 0, 15, 30, and 60 min after drug administration. From the observed data the maximum possible effect in percentage of increased tail withdrawal latency at 60 min is calculated for each group.

Maximal possible effect (MPE) in tail withdrawal latency in percentage (%) at 60 min was calculated in Pentazocine 6, 12 mg/kg, Morphine 1 mg/kg and combination group (Pentazocine 3 mg/kg + Morphine 0.1 mg/kg) (53.76 ± 8.36 , 78.86 ± 5.05 , 91.66 ± 3.04 , 58.15 ± 3.96 respectively) which is more and statistically significant in comparison to control group (3.38 ± 1.23) (Table no.2). These results suggest that Pentazocine 6, 12 mg/kg, Morphine 1 mg/kg and combination group can produce significant antinociceptive effect. Further intergroup comparison of MPE (%) shown that Pentazocine 12 mg/kg (78.86 ± 5.05) is comparable with Morphine 1 mg/kg (91.66 ± 3.04) (Table no.2), indicating that Morphine is more potent than Pentazocine. MPE (%) combination group (58.15 ± 3.96) is significantly more than Pentazocine 3 mg/kg (11.84 ± 1.65) alone or Morphine 0.1 mg/kg (5.49 ± 0.82) alone indicating Pentazocine can potentiate antinociceptive effect of Morphine (Table no.3 and 4).

SL. NO	NS	MOR 0.1	MOR 1	PTZC 3	PTZC 6	PTZC 12	PTZC 3+MOR 0.1
1	4.16	6.66	91.66	12.5	13.04	58.33	50
2	4	4.34	100	12	68	82.6	50
3	4.16	4.16	83.33	12.5	60	75	66.66
4	8	4.34	91.66	4.34	66.66	91.3	41.66
5	0	4.34	100	13.04	58.33	75	66.66
6	4.16	9.09	83.33	16.66	56.52	90.9	73.91
Total	24.48	32.93	549.98	71.04	322.55	473.13	348.89
Mean	4.08	5.49	91.66	11.84	53.76	78.86	58.15
SD	2.53	2.00	7.46	4.05	20.47	12.37	12.63
SE	1.03	0.82	3.04	1.65	8.36	5.05	5.16

NS – Normal Saline, MOR – Morphine, PTZC – Pentazocine

Table 3: MPE% of increased tail withdrawal latency

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Figure 2: Graph showing MPE of increased tail withdrawal latency in % of normal saline, Morphine, Pentazocine and combination groups.

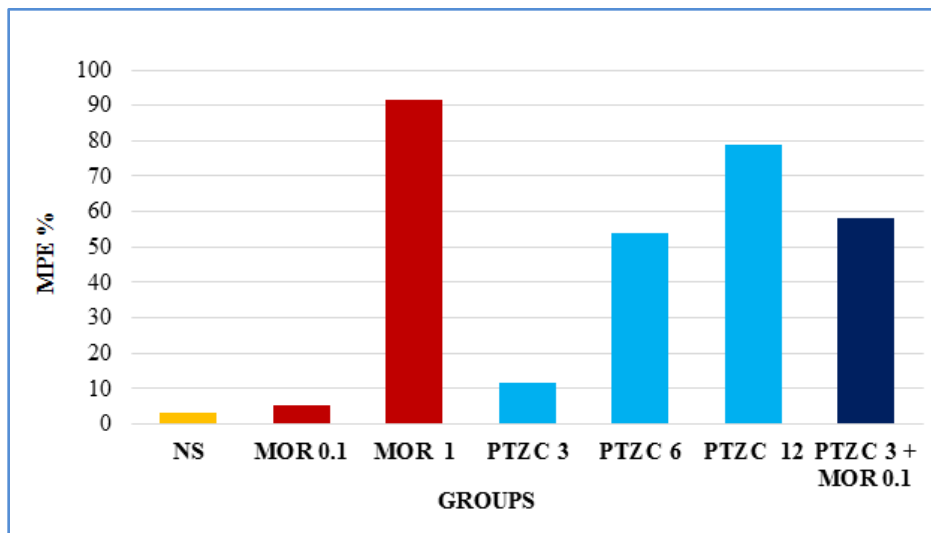


Figure 2

Comparison between different groups	Mean Difference	p Value
NS vs MOR 0.1	-2.10	.738 ns
NS vs MOR 1	-88.27	<.0001***
NS vs PTZC 3	-8.45	.184 ns
NS vs PTZC 6	-50.37	<.0001***
NS vs PTZC 12	-75.46	<.0001***
NS vs PTZC 3 + MOR 0.1	-54.75	<.0001***

NS-Normal Saline, MOR-Morphine, PTZC- Pentazocine
ns-not significant, **** Highly Significant

Table 4: Intergroup comparison of MPE in % of Pentazocine Tail withdrawal latency by multiple comparison (LSD) test

DISCUSSION & CONCLUSION: Pentazocine (6, 12 mg/kg, i.p)(morphine 1mg/kg i.p) produced significant antinociceptive effect in rat tail flick and tail immersion models. Pentazocine 3 mg/kg (sub-antinociceptive dose) produced significant antinociceptive effect when given in combination with morphine 0.1 mg/kg (sub-antinociceptive dose). Onset of antinociception is rapid with morphine than pentazocine. Morphine is more potent than pentazocine for producing antinociceptive effect in rat tail flick and tail immersion models.

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